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PREVENTION OF POST-METRONIDAZOLE CANDIDOSIS WITH AMPHOTERICIN B PESSARIES*

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Trichomonas vaginalis and *Candida albicans* are the two organisms most commonly responsible for an excessive irritating vaginal discharge (Danezis and Marsellou, 1960). It has been suggested that in the last few years, as a result of the widespread use of antibiotics, *Candida* infection has become the principal cause of vulvovaginitis (Rohatiner, 1966; Rohatiner and Grimble, 1967). Metronidazole has also been incriminated in this way. Vaginal candidosis developed during treatment in three of 42 women treated with the drug by Moffett and McGill (1960), giving rise in two cases to severe or moderately severe symptoms. The number of patients with *C. albicans* demonstrated in the vaginal discharge after treatment with metronidazole increased by 24·5 per cent. in 102 cases treated by Keighley (1962), by 19 per cent. in 100 treated by Beveridge (1962), by 11 per cent. in 101 treated by Csonka (1963), and by 4·4 per cent. in 69 treated by Brochin and Buxton (1963). On the other hand neither Rees (1960) nor Rodin, King, Nicol, and Barrow (1960) found any evidence to suggest that the drug favoured or inhibited the growth of *Candida* species.

In an attempt to prevent post-metronidazole candidosis, Beveridge (1964) prescribed a Nystatin pessary to be inserted nightly during the week metronidazole was taken; she succeeded in reducing the post-treatment incidence of fungus infection from 19 to 7 per cent., but considered the result disappointing.

In this paper the results are reported of a similar attempt, using pessaries containing 50 mg. amphotericin B, a polyene antifungal antibiotic reported to be more active *in vitro* against *Candida* species than Nystatin (Ewing, 1967). In clinical trials amphotericin B (Fungilin) was reported by Ewing (1967) to be successful in eliminating *Candida* from the vagina in about 80 per cent. of cases treated with one pessary nightly for 14 days. Although similar results, a cure rate of 78 per cent., were attained by Csonka (1967), he found Nystatin somewhat more effective when comparing the effect of one amphotericin B pessary with that of two Nystatin pessaries inserted nightly for 15 days.

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Clinical Material and Methods

At the Venereal Diseases Clinic, St. Luke's Hospital, Bradford, during a period of 4 months in 1966 and one of 5 months in 1967 (with an interval of 7 months during which the clinic was under reconstruction), 113 women were found at some stage of their attendance to have a trichomonal infestation. *T. vaginalis* was identified in the vaginal secretion by wet smear examined microscopically by direct light, by culture, or by a Papanicolou-stained smear in those cases in which specimens for routine cytological screening were collected at the same time. High vaginal swabs were submitted in non-nutrient transport medium to the laboratory where the growth medium (Oxoid Trichomonas medium No. 2) was inoculated for both *T. vaginalis* and *C. albicans*. Similar methods of identification of the two organisms were used at follow-up examinations.

As soon as the diagnosis of trichomoniasis was established, treatment was started as follows: 58 women were given a supply of metronidazole (Flagyl) comprising 21 200-mg. tablets to be taken 8-hourly for one week (first group), and 53, who were seen at one of four selected clinical sessions, were given in addition seven 50-mg. amphotericin B vaginal pessaries, one to be inserted each night during that week (second group).

Table I (overleaf) shows the duration of the follow-up period.

Eighteen women did not return after treatment, leaving for assessment 51 in the first group and 42 in the second.

Irrespective of the length of the follow-up period, 30 patients attended only once from 7 to 32 days after completing treatment, 29 had two follow-up examinations, twenty had three, and fourteen had four or more.

TABLE I
LENGTH OF FOLLOW-UP AFTER TREATMENT

Follow-up	Number of Patients Treated	
	Metronidazole	Metronidazole + Amphotericin B
No further attendance	7	11
Up to 2 wks	13	3
2 wks to 1 mth	21	10
1 mth to 2 mths	13	10
3 mths	4	19
Total assessable	51	42

The age groups and marital status of the 93 patients are shown in Table II. Two women, one in each group, were taking oral contraceptives. Eight women in the first group and six in the second were pregnant. There were no cases of glycosuria.

TABLE II
AVERAGE AGE AND MARITAL STATUS OF PATIENTS
(per cent.)

Treatment		Metronidazole		Metronidazole + Amphotericin B	
		No. in Group	Average Age	No. in Group	Average Age
Age Group (yrs)	Under 20	14	17·9	11	17·8
	20–29	28	24·3	18	23·9
	30–39	7	33·3	11	34·1
	40–49	2	44·5	2	44·0
	Total	51	24·5	42	25·6
Marital Status	Single	30	58·8	21	50
	Married	13	25·5	11	26·2
	Divorced / Separated / Widowed	8	15·7	10	23·8
	Total	51	100·0	42	100·0

Fifty-one patients had a gonococcal infection and in 26 cases (15 in the first group and 11 in the second) the diagnosis of gonorrhoea was established on the same occasion as that of trichomoniasis; these 26 patients received anti-gonorrhoeal treatment during the period metronidazole was taken. Eight (in 1966) were given one dose and thirteen (in 1967) two doses on successive days of 1·2 mega-units aqueous procaine penicillin (the routine clinic treatment for women with gonorrhoea in the respective years); four were treated with single injections of 2 g. cephaloridine and one with an injection of 2 g. kanamycin.

Results

The initial laboratory findings and the incidence of *Candida* in the vaginal secretions before and after treatment are shown in Table III.

In the group treated with metronidazole alone, *Candida* was detected before treatment in five cases; after treatment it was found in fifteen, including

TABLE III
LABORATORY FINDINGS BEFORE AND AFTER TREATMENT

Initial Laboratory Findings	Metronidazole		Metronidazole + Amphotericin B	
	No. of Swabs	Percentage	No. of Swabs	Percentage
T. vaginalis only	31	60·8	22	52·4
T. vaginalis + Gonococci	15	29·4	11	26·2
T. vaginalis + *Candida albicans*	5	9·8	8	19·0
T. vaginalis + Gonococci + *Candida albicans*	—	0	1	2·4
Total	51	100·0	42	100·0
Candida before Therapy	5	9·8	9	21·4
Candida after Therapy	15	29·4	6	14·2
Effect of Therapy on *Candida*	10 Increase	19·6	3 Decrease	7·2

three of those with pre-treatment evidence of the fungus. Three women had symptoms and clinical evidence of *Candida* infection (pruritus vulvae and inflammation of the vulva and vagina with profuse cheesy vaginal discharge); in only one of them, a pregnant woman, was the fungus detected before treatment, but one other had been treated for vaginal candidosis 4 months previously. These three women required treatment and were successfully treated with amphotericin B pessaries inserted nightly for 15 days.

In the group treated with metronidazole in conjunction with pessaries, *Candida* was detected before treatment in nine women and after treatment in six women, three of them pregnant. The fungus was found both before and after treatment in only one case. None of the women in this group showed clinical evidence of *Candida* infection.

Seven of the 21 patients with post-treatment occurrence of *Candida* had been treated for gonorrhoea initially, six with penicillin and one with cephaloridine, which was more or less in proportion to the total number under study. In the woman in the first group who was taking the contraceptive pill, *Candida* was found after but not before treatment; in the woman on oral contraceptives in the second group, *Candida* was absent throughout.

Discussion

Winner (1966) defines *Candida* as yeast-like fungi which frequently inhabit the human body without causing disease, which occasionally cause mild disease, and which rarely cause serious disease. The reported frequency of occurrence of *Candida*

in the vagina varies widely. Pickhardt and Breen (1957) compiled reports from eleven investigators which gave the incidence of vaginal candidosis with and without symptoms as ranging from 0·08 to 61·7 per cent. in non-pregnant women and from 0·74 to 66·7 per cent. in pregnant women; the average was 17·6 per cent. in a total of 13,450 non-pregnant and 30·2 per cent. in a total of 5,305 pregnant women. These figures are somewhat higher than the 16 and 25 per cent. in non-pregnant and pregnant women respectively quoted by Winner (1966) as "typical British figures" for the occurrence of *C. albicans* in vaginal swabs received in a clinical microbiology department from hospital patients most of whom were not suspected of suffering from *Candida* infection.

The different rates of incidence of *C. albicans* in the vaginal secretion before and after treatment with metronidazole, with or without amphotericin B pessaries, appear to be of no practical significance. One would expect the incidence of *Candida* in the vaginal secretion to be low in the presence of *T. vaginalis,* which thrives at a higher pH than the fungus (Boycott, 1961), and to tend to increase after the protozoon has been eliminated by treatment though remaining low if a fungicidal agent was given concurrently. In both groups of this series, in some cases *Candida* was found before but not after treatment, and in others *vice versa.* In those patients who had repeated post-treatment examinations the findings were not always consistent, depending probably on the phase of the menstrual cycle at which the swab was taken, the one taken during the premenstrual phase being the most likely to yield a growth of the fungus (Whitehouse and Porteous, 1962). It is possible that the chances of symptoms of vaginal candidosis developing under the influence of metronidazole are increased when treatment coincides with the premenstrual phase. It is doubtful whether the small proportion of cases in which the drug gives rise to such symptoms justifies the routine prophylactic prescription of antifungal pessaries. The procedure may be advisable in the presence of conditions such as pregnancy or diabetes, in which *C. albicans* is known to proliferate; it may also prevent a relapse, in the cases of women with a recent history of vaginitis due to *Candida* infection.

Summary

In an attempt to prevent vaginal candidosis developing after the treatment of trichomoniasis with metronidazole, 53 women were given one 50 mg. amphotericin B pessary each night for 7 days in addition to metronidazole 200 mg. 8-hourly for the same period. For comparison, 58 women with trichomoniasis were treated with metronidazole alone. 42 of those receiving the combined treatment and 51 of those receiving metronidazole alone were available for assessment.

The percentage of vaginal swabs from which *C. albicans* was cultured decreased by seven after combined treatment and increased by nineteen after treatment with metronidazole alone. In the last group three patients, including one pregnant woman and one who had been treated for vaginal candidosis 4 months previously, showed clinical evidence of *Candida* infection.

Although amphotericin B pessaries given in conjunction with metronidazole effectively prevent post-treatment candidosis, considering that the fungi frequently inhabit the vagina without giving rise to symptoms, routine antifungal treatment seems not to be justified, except in the presence of conditions in which *C. albicans* proliferates (such as pregnancy and diabetes) and also in cases of recent vaginal candidosis.

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La prévention de la candidose post-métronidazole par les comprimés vaginaux d'amphotéricine B

Résumé

Dans une tentative d'empêcher la candidose vaginale de se développer après le traitement de la trichomoniase par le métronidazole, 53 femmes ont reçu un comprimé vaginal de 50 mg. d'amphotéricine B chaque soir pendant 7 jours en plus de 200 mg. de métronidazole à intervalles de 8 heures pendant la même période. En comparaison, 58 femmes atteintes de trichomoniase ont été traitées avec le métronidazole seul; 42 des femmes recevant le traitement combiné et 51 des femmes recevant métronidazole seul étaient disponibles pour l'évaluation.

Le pourcentage des prélevements vaginaux donnant des *C. albicans* en culture a diminué de sept après le traitement combiné et a augmenté de dix-neuf après le traitement avec le métronidazole seul. Dans le dernier groupe, trois malades, y compris une femme enceinte et une qui avait été traitée pour une candidose vaginale 4 mois auparavant, avaient montré des signes cliniques d'une infection par le *Candida albicans*.

Bien que les comprimés vaginaux d'amphotéricine B donnés en conjonction avec le métronidazole empêchent efficacement la candidose après le traitement et considérant que la levure est fréquemment présente dans le vagin sans donner lieu à des symptômes, un traitement routinier anti-muguet ne semble pas être justifié sauf dans certains conditions favorisant la prolifération du *C. albicans* (telles que la grossesse et le diabète) et aussi dans les cas de candidose vaginale récente.